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TI Metabolism of daidzein and genistein by intestinal ***bacteria***
AU Chang, Yu-Chen; Nair, Muraleedharan G.
CS Bioactive Natural Product Lab., Michigan State Univ., East Lansing, MI, 48824, USA
SO J. Nat. Prod. (1995), 58(12), 1892-6

Lignans and isoflavonoids
AU Adlercreutz, H.
CS Department of Clinical Chemistry, Meilahti Hospital, University of Helsinki, Helsinki, FIN-00290, Finland
SO COST Action 92, Diet. Fibre Ferment. Colon, Proc. COST Action 92 Workshop (1996), Meeting Date 1995, 324-332. Editor(s): Maelkki, Yrjoe; Cummings, [illegible] Luxembourg.

Differential effects of dietary phyto-estrogens daidzein and ***equol*** on human breast cancer MCF-7 cells
AU Sathyamoorthy, N.; Wang, T. T. Y.
CS Laboratory of Nutritional and Molecular Regulation, NCI-Frederick Cancer Research and Development Center, Frederick, MD, 21702-1201, USA
SO Eur. J. Cancer (1997), 33(14), 2384-2389

Urinary ***equol*** excretion with a soy challenge: influence of habitual diet
AU Lampe, Johanna W.; Karr, Susan C.; Hutchins, Andrea M.; Slavin, Joanne L.
CS Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA
SO Proc. Soc. Exp. Biol. Med. (1998), 217(3), 335-339
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LIGNANS AND ISOFLAVONOIDS

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SUMMARY

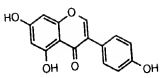
A short review dealing with the origin, intestinal metabolism, biological effects and role in cancer prevention of lignans and isoflavonoid phytoestrogens is presented. These compounds occur in fibre-rich food like whole-grain products, seeds, (particularly linseed), fruits, berries, and in both soy beans and purified soy protein products. The precursors in food are converted to biologically active compounds by gut bacteria. For the isoflavonoids, mainly occurring in soy products and clover, only hydrolysis of the glycosidic bond is necessary to convert them to the active compounds genistein and daidzein, the latter being further metabolized to equol. In purified soy products genistein and daidzein are already present as such and no gut bacterial metabolism is needed for absorption. The lignan precursors are matairesinol and secoisolariciresinol and from these compounds the intestinal bacteria have to remove the carbohydrate and two methyl and two hydroxyl groups before they are converted to the biologically active enterolactone and enterodiol.

1. INTRODUCTION

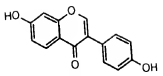
In Asian countries such as Japan and China the incidence of prostate, breast and colon cancer is low compared to that in the Western world, particularly compared to USA. In Finland the incidence of these cancers is lower than in USA, but clearly higher than in Japan, but the rate is steadily increasing both in Japan and in Finland. Differences in fat consumption, originally being very low in Japan, explain some of the differences in incidence between Japan, and the West-European countries and USA, but they do not explain the incidence differences between Finland and USA because of the similar animal fat consumption in these countries. It seems obvious that in addition to causative factors, protective factors in the diet may play an essential role.

2. LIGNANS AND ISOFLAVONOIDS, TWO GROUPS OF CANCER-PROTECTIVE COMPOUNDS

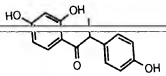
The detection and identification in human urine and other biological fluids of the two groups of hormone-like compounds, the lignans and isoflavonoids (1-5), and the observation that their excretion showed a positive correlation with fibre intake (6) and a negative correlation with the incidence of the above-mentioned cancers, led us to formulate a hypothesis according to which these compounds, originating in the diet, may play a protective role with regard to many Western diseases (4, 5, 7-11). The isoflavonoids, occurring in high amounts in soybeans and soy products, and the



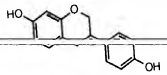
Genistein



Daidzein

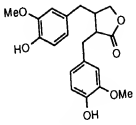


O-Demethylangolensin

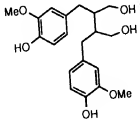


Equol

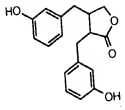
Isoflavonoids



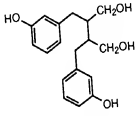
Matairesinol



Secoisolariciresinol



Enterolactone



Enterodiol

Lignans

Fig. 1. Structures of some isoflavonoids and lignans.

lignans, derived mainly from whole grain bread, various seeds, fruits, berries and vegetables, have been shown to influence not only sex hormone metabolism and biological activity but also intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation and angiogenesis. Most of these effects suggest that they may inhibit cancer growth but may also prevent cancer initiation.

The pioneers in the phytoestrogen research worked in the veterinary field. They observed great fertility problems (12), particularly in sheep but also in cattle, as a result of consumption of forage plants, mainly clover and alfalfa, containing high amounts of phytoestrogens (13-15). The infertility in sheep is brought about by many factors, among other by interference with spermatozoa in the genital tract, abnormal transport of ova, [illegible] with implantation and decreased sensitivity of the hypothalamic-hypophyseal system to feedback regulation by estradiol. It is therefore somewhat surprising, that such problems have not been reported to any significant degree in human vegetarian subjects or Japanese consuming high amounts of phytoestrogen-containing foods. Lindner in his review in 1976 (13) in fact stated that "there is no published evidence that herbal estrogens reaching the human from any of these sources is of pathogenic significance". Until 1981-84 it seems that nobody had suggested that the phytoestrogens could be beneficial for human health. In opposite many relatively recent publications suggest that some environmental estrogens, including the phytoestrogens, could have negative effects in man (16, 17).

The detection of an unknown cyclically occurring compound in urine of a female green monkey, and later in human urine independently by two groups led to the identification of the two mammalian lignans, enterolactone and enterodiol, (2, 3) and later on to the identification of equol and many other metabolites of these diphenols (4, 5, 18-21). The main sources of lignans are various seeds like linseed (secoisolariciresinol), sesame seed (matairesinol) and various grains (matairesinol and secoisolariciresinol), and also whole soybeans. Isoflavonoids occur mainly in soybeans and various soy products (tofu, soy milk, miso) (genistein and daidzein, free or as glycosides), except soy sauce, and to a lesser extent in other legumes. Recently we found that tea contains both secoisolariciresinol and matairesinol in relatively high amounts.

The precursors of the isoflavonoids found in the human organism occur in plants as glycosides and the gut bacteria are responsible for the hydrolysis of these compounds. In addition to the two main compounds genistein and daidzein (formed from the corresponding glycosides genistein and daidzein), many biologically active metabolites are formed (19, 22) probably mainly by the influence of gut bacteria. In sheep and chimpanzees equol formation seems to be high, but in human subjects it is relatively low, in some subjects equol is hardly detectable in plasma even despite relatively high soy consumption. This could be an explanation why no negative effects of soy intake in human subjects have been observed although equol is the cause of clover disease in sheep (12-15). Purified soy protein products (tofu, miso, soy protein meal) contain most of the genistein and daidzein in the free form and no gut bacteria are needed for their absorption. Subjects with only a very short colon and a great part of the small intestine removed due to cancer, still absorb considerable amounts of isoflavonoids from soy protein products. Both plant lignans and isoflavonoids are phytoalexins protecting the plant and particularly the seeds against fungi, viruses and bacteria and may also exert these effects in the human intestine. The lignan precursors (matairesinol and secoisolariciresinol) in grain seem to occur in the aleurone layer of the grain. This layer of 1-3 cells is very tightly bound to the outer fibre layer and is not present any more in refined meal products. After removal of two methyl and two hydroxyl groups the plant lignans matairesinol and secoisolariciresinol are converted to the two main mammalian lignans, enterolactone

and enterodiol, respectively. Enterodiol is then partly oxidized to enterolactone (19, 20).

3. BIOLOGICAL EFFECTS OF LIGNANS AND ISOFLAVONOIDS

All of these compounds are weakly estrogenic and bind with low or very low affinity to the estrogen receptor (19, 23). Due to their estrogenicity they stimulate in liver cell cultures the production of sex hormone binding globulin (SHBG) (24, 25). The effect on SHBG production is probably caused by stabilizing the SHBG mRNA (Loukovaara *et al.*, submitted for publication). A higher plasma SHBG reduces the clearance and uptake of estradiol and testosterone into the cells which leads to lower biological activity of the sex hormones and theoretically lower breast and prostate cancer risk. The excretion of lignans and isoflavonoids in urine correlates significantly with plasma SHBG levels (24), and vegetarians have relatively high and many but not all breast cancer patients usually low SHBG levels.

The most interesting biological activities of these compounds are their antiproliferative and anticarcinogenic activity. This has been demonstrated in many *in vitro* cell culture and *in vivo* animal studies (reviews in 20, 21). Some lignans and isoflavonoids bind to the nuclear type II binding sites and may in this way exert an antiproliferative effect regarding cells stimulated by estradiol (26). The isoflavonoid genistein, the most interesting of these compounds because of its high concentration in plasma and urine of Japanese subjects (27, 28), is a tyrosine-kinase, angiogenesis, and topoisomerase II inhibitor and stimulates differentiation in many types of cells including leukemia cells (ref. in 11, 21, 29). It antagonizes the effect of epidermal growth factor and other growth factors. Genistein inhibits proliferation of numerous different types of malignant cells in culture, but relatively high concentrations are needed. Many cells are stimulated at lower concentrations and the possible cancer protective role of genistein *in vivo* in human subjects is still uncertain. Soy products fed to rats or mice inhibit breast cancer growth. In cell cultures, in the presence of estradiol, physiological concentrations of enterolactone antagonize estradiol with regard to breast cancer cell growth (24). In addition, enterolactone is a moderate aromatase inhibitor entering the cells and inhibiting aromatase both in choriocarcinoma cells as well as in preadipocytes (30-32). All the compounds are antioxidative, particularly genistein. Consequently these compounds may contribute to the prevention of other chronic diseases like coronary heart disease and may in the gut also prevent oxidation of cocarcinogens to carcinogens (see below).

4. LIGNANS AND ISOFLAVONOIDS, AND BREAST AND PROSTATE CANCER

The observation of very low urinary excretion of lignans and equol in postmenopausal breast cancer patients (4) compared to vegetarians, and very high excretion in chimpanzees, highly resistant to the induction of breast cancer by various toxic compounds, and in Japanese subjects with very low breast and prostate cancer rates, led us to suggest that these compounds may be protective with regard to hormone-dependent cancer and also colon cancer (4, 5, 8, 33). The toxicity of these compounds in a certain species seems to depend on the ability to metabolize them. It has been observed that in cheetahs, who like other cats have low glucuronidation activity, soy-containing food causes liver damage leading to infertility (34). The male chimpanzee in caption excretes 250-300 µmol/l of equol in urine, compared

to about 0.5 μmol/l in Japanese men and women and less than 0.1 μmol/l in subjects consuming a Western diet (measured by combined gas chromatography-mass spectrometry). In human subjects the highest isoflavonoid values are observed in Japanese men and women, in macrobiotics and vegans followed by lactovegetarians. Omnivorous subjects have usually very low values. Oriental immigrants to Hawaii have already within a few months low isoflavonoid values in urine. In Finland lignan excretion tends to be the highest in North Karelian subjects with less cancer risk, less in subjects living in Helsinki and the lowest values are found in breast cancer patients and some omnivorous subjects. The lignan excretion is higher in Finland compared to USA, but in Japan we found the lowest values in urine. However, in plasma, the biologically active sulfates and free fraction was similar or even higher in some Japanese compared to Finnish men. This was obviously due to less glucuronidation in the Japanese subjects, because their plasma concentration of lignan glucuronides was very low. Thus the Japanese have relatively high concentrations of the sulfates and free fraction of both plasma isoflavonoids and lignans.

Despite of the same incidence of latent and small or non-infiltrative prostate carcinomas as in the Western countries (35) the mortality of Japanese men in prostate cancer is very low. Decreased prostate cancer risk has been found in men of Japanese ancestry in Hawaii (36) who eat rice and tofu, a soybean product containing isoflavonoids in great quantities (27). That diet may be an important factor in the promotional stage of the disease is shown in two studies (37, 38) suggesting that environmental factors later in life can have a substantial impact on the likelihood of developing clinically detectable prostate cancer. Despite of the high fat intake the prostate cancer incidence in Finland and some European countries like France is much lower than in USA, but much higher than in Japan. Because prostate cancer is hormone-dependent we have postulated, that the diet in countries with low or relatively low cancer risk may contain higher amounts of cancer-protective compounds affecting hormone metabolism or action (11). Among such compounds lignans and isoflavonoids seem of particular interest because their close structural relationship with estrogens. In addition, various other types of flavonoids may be of interest in this connection.

Using the developmentally estrogenized mouse model, it has been shown that the development of dysplastic changes in prostate was delayed by soy feeding. When animals were given soy-free diet from fertilization onwards, most of them had dysplastic lesions at the age of 9 months, but in a group given soy diet the number of animals showing prostatic dysplasia was significantly lower. At the age of 12 months, the difference between the two groups had diminished and was not any more statistically significant (39, 40). Morphologically these dysplastic lesions are similar to prostatic intraepithelial neoplasia (PIN) in the human prostate. Although no progression to carcinomas with invasion to surrounding tissues or metastasis can be demonstrated, the tissue changes, observed in developmentally estrogenized mice, suggest an increased potential for benign and malignant growth. Soy also prevents prostatitis in rats (41).

The early observation of the low grain fibre intake combined with a very low excretion of lignans in urine of postmenopausal breast cancer patients living in Boston MA (USA) suggested that the lignans may play a role as protective compounds in breast cancer. As already mentioned the lignans have been shown to inhibit estrogen-stimulated proliferation of human MCF-7 breast cancer cells in culture, but only at physiological levels. Lignans cannot antagonize very high estrogen levels and surprisingly they stimulate breast cancer cells in the absence of estradiol in cell cultures *in vitro*. At high lignan level the antagonizing effect cannot any more be observed *in vitro*. Lignans are moderate inhibitors of the aromatase enzyme and bind to the type II nuclear estrogen-binding site. Furthermore, they seem

to stimulate SHBG synthesis. All these biological activities may reduce breast cancer risk. Even more data, both *in vitro* and *in vivo*, is available suggesting a protective effect of isoflavonoids with regard to breast cancer (21). Feeding of soy to experimental animals reduces breast cancer risk and treatment with genistein postpartum in rats reduces the development of mammary tumors when dimethylbenz(a)anthracene was administered after genistein treatment (42). A precocious maturation of undifferentiated terminal end buds to more differentiated lobules may account for neonatal genistein treatment protecting against chemically induced mammary cancer. Epidemiological evidence obtained in Singapore indicates that soy intake is associated with lower breast cancer risk in women (43).

5. LIGNANS, ISOFLAVONOIDS AND COLON CANCER

In 1984 the author suggested that the lignans may be protective with regard to both breast and colon cancer (8). Recently, we observed a high lignan excretion in subjects with a low risk of colon cancer (see discussion, 44). Lignan excretion is also high in Finnish subjects (45) living in areas with lower colon cancer risk. Epidemiological evidence obtained in Japan (46) points to lower colon cancer incidence in areas with high tofu consumption. This is now being further investigated. Both breast and colon carcinogenesis is reduced in rats fed flax seed containing high amount soy secoisolariciresinol (47, 48). Due to their phenolic structure, lignans and flavonoids have antioxidative properties (8, 49-51) and may prevent conversion of procarcinogens to carcinogens or eliminate free radicals in the gut reducing colon cancer risk.

6. OTHER ANTICANCER EFFECTS OF GENISTEIN

Synthetic genistein and extracts from human urine containing genistein have been shown to inhibit the growth of cells from solid pediatric tumors like neuroblastomas (with both normal and enhanced MYCN expression), rhabdomyosarcomas, and Ewing´s sarcomas (52). Such extracts and synthesized genistein inhibited bFGF - stimulated endothelial cell (bovine brain-derived capillary endothelial cells) proliferation and in vitro angiogenesis (29). Genistein reduces the production of plasminogen activator and plasminogen activator inhibitor-1 (29) in cloned bovine microvascular endothelial cells from the adrenal cortex. Genistein also inhibits the growth of gastric cancer cells (53) and stimulates differentiation in many malignant cells including melanoma cells (54). Genistein seems to modulate decreased drug accumulation in non-P-glycoprotein mediated multidrug resistance (55).

7. CONCLUSIONS

Plant food that contains isoflavonoids and lignans may play a role in the prevention of several types of cancer and particularly the so-called Western cancers. The concentrations in plasma of these compounds, particularly the lignans, may easily reach biologically active levels without toxic effects. By inhibiting the effect of growth factors and angiogenesis, genistein may be a general inhibitor of cancer growth. To call soy isoflavonoids the natural equivalent to the breast cancer antiestrogen drugs as suggested by others, is in my opinion not indicated on the basis of our present knowledge. This is mainly due to their different mechanisms of action.

Genistein also stimulates differentiation of many types of leukemic cells and affects cell cycle. By modulating drug transport, genistein may prove to be a good addition to established cancer therapy. Lignans on the other hand seem in the light of recent research to be at least as potent as isoflavonoids in preventing initiation and promotion of cancer and may perhaps be used also in connection with cancer therapy. The biological effects described may be used as a preventive strategy for other Western diseases not discussed in this connection, such as cardiovascular diseases and osteoporosis, due to the antioxidative and estrogenic effects. It should be kept in mind that it is to be preferred to consume original food, or food modified only slightly, instead of consuming isolated or synthetic compounds. This is particularly true for the lignans. The evidence obtained this not yet sufficient for any specific dietary recommendations (*e.g.* kind of food, amount per day) and further work is needed to establish the role of these natural anticancer compounds in human health and disease. However, present dietary recommendations are to a large extent in good agreement with the results of recent phytoestrogen research.

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